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IRB Protocol- Hydrocortisone and Fludrocortisone versus Hydrocortisone Alone in Critically Ill Medical Patients with Septic Shock

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Background and Rationale:

Fludrocortisone is a synthetic adrenocortical steroid that mimics the endogenous activity of aldosterone, resulting in an enhanced reabsorption of sodium ions in the distal tubule of the kidney and resultant increased extracellular fluid volume. The goal of fludrocortisone therapy is to increase blood pressure by increased extracellular volume and potential vasoconstrictive activity. Hydrocortisone, another steroid studied in conjunction with fludrocortisone in septic shock patients, displays both mineralocorticoid and glucocorticoid activity, unlike fludrocortisone which has all mineralocorticoid activity. In septic shock patients that present with a potential adrenal insufficiency due to impaired glucocorticoid and vasopressin production, it is not clear whether treatment with hydrocortisone alone or in combination with fludrocortisone provides any difference in mortality and morbidity.

In general, low dose, physiologic dosed steroid use has consistently shown to reduce vasopressor requirements, but mortality benefit remains controversial despite multiple randomized, controlled trials (RCTs). Recent meta-analyses have concluded that uncorrected data do not demonstrate mortality benefit[1]. Of the main RCTs conducted in the past 20 years, there are two main differences between those that find mortality benefit with steroid use (APROCCHSS and Ger-Inf-05) and those that do not (CORTICUS, HYPRESS, and now ADRENAL). The first difference is the use of fludrocortisone in combination with the standard dose of hydrocortisone 200 mg intravenously (IV) daily. The second difference is the focus on patients with septic shock who did not improve after initial resuscitation and were requiring higher baseline doses of vasopressors. The trials finding mortality benefit enrolled sicker patients at baseline than the trials that did not find mortality benefit, which was identified through a variety of severity scores (APACHE, SAPSII, and SOFA) and baseline mean vasopressor doses[2,3]. For example, baseline SOFA scores were on average 12 in the treatment arm of the APROCCHSS trial versus 10.6 in the CORTICUS trial[3,4]. In addition, mean norepinephrine doses at randomization in the ADRENAL trial were 30 mcg/min, whereas the mean norepinephrine dose at randomization in the APROCCHSS trial was 1 mcg/kg/min (70 mcg/min in a 70 kg patient)[3,5].

The theory for use of fludrocortisone centers around data that suggests 40-65% of critically ill patients have high plasma renin activity and low plasma aldosterone concentrations[2]. Moreover, experimental sepsis studies in murine models have suggested that a marked NF-kB mediated down-regulation of mineralocorticoid receptors occurs during the

shock process. Administration of aldosterone in mice resulted in improved response to phenylephrine[6]. Based on the RCTs performed in human subjects, however, it is controversial whether addition of fludrocortisone provides any true benefit in refractory septic shock patients. Moreover, to date there has not been a trial, whether retrospective or prospective, that has directly compared the use of hydrocortisone alone versus the combination of hydrocortisone and fludrocortisone. Because of this lack of data, we will be investigating the use of hydrocortisone alone versus the combination in critically ill septic shock patients admitted to the medical intensive care unit. Currently, both are considered standard of care both within and outside of the University of Tennessee Medical Center Knoxville.

Objective: To determine if the use of hydrocortisone plus fludrocortisone is associated with a faster resolution of shock (defined as 24 hours vasopressor free) when compared to the use of hydrocortisone alone in medical, critically ill septic shock patients i

Study Design and Methods:
This study is a single-center, prospective, open-label, randomized trial which will evaluate adult patients admitted with septic shock to the medical critical care unit (MCC).

Inclusion Criteria:

- Age ≥ 18
- Critically ill medicine patients requiring addition of stress dose steroid therapy (hydrocortisone) in addition to pressors for septic shock management during their ICU stay
- Fludrocortisone administered within 24 hours after initiation of hydrocortisone if in combination therapy group

Exclusion Criteria:

- Use of fludrocortisone and/or hydrocortisone for any reason other than septic shock management during ICU stay
- Fludrocortisone/hydrocortisone initiated by any service other than critical care medicine
- Prior use of fludrocortisone/hydrocortisone at time of admission (home or outside facility)
- Patients not appropriate for study inclusion as determined by provider discretion
- Patients receiving steroid therapy not in accordance with assigned group per location (MCC1 or MCC2)
- Patients re-admitted to the MCC during the same admission and restarted on vasopressor therapy will be noted during data collection and only the initial admission will be included for analysis
- Any patient receiving greater than one dose of hydrocortisone 100 mg
- Physical or medical contraindication to receiving PO or PER FT (per feeding tube) fludrocortisone.

Protocol:
All patients admitted to the medical critical care unit side 1 (MCC1) or side 2 (MCC2) will be provided a "Notice of Research." At any time, refusal or withdrawal from the study can be requested by the patient, patient advocate, or provider.

Patients that meet inclusion criteria for the study will receive either hydrocortisone 50 mg IV Q6h alone or a combination of hydrocortisone 50 mg IV Q6h plus fludrocortisone 50 mcg PO/PER FT daily. Fludrocortisone must be initiated and administered within 24 hours after the first administered dose of hydrocortisone. Because fludrocortisone is only available as a 100 mcg tablet, the nurse at the bedside will split the tablet into two as to provide a 50 mcg dose. This is standard of practice currently when fludrocortisone is utilized in our institution.

Steroid therapy assignments will be randomized based on patient location. For three consecutive months starting in October 2018, all patients in MCC1 will receive hydrocortisone alone and all patients admitted to MCC2 will receive hydrocortisone plus fludrocortisone. Then, in the following three consecutive months, this will be flipped and MCC1 will receive hydrocortisone plus fludrocortisone while MCC2 will receive hydrocortisone alone. This change in group assignments will occur to account for the difference in number of beds between MCC1 and MCC2, and to minimize the potential differences in patient acuity by location.

Initiation of hydrocortisone for inclusion in the study will be determined solely by provider discretion as the standard of care for septic shock patients. Once hydrocortisone is initiated, fludrocortisone will be initiated within 24 hours for patients on the qualifying side of the unit, unless any of the previously stated exclusion criteria are present. Because these interventions are currently utilized and considered standard of care in the MCC, data collection will be performed retrospectively by generating a list of patients in the MCC receiving hydrocortisone therapy.

While each included patient's data will be recorded retrospectively after randomization, we do believe that it is necessary to perform this study in a prospective manner rather than fully retrospective. It is not feasible to perform this study retrospectively as we would not be able to ensure adequate and equal numbers in each group within the medical critical care unit, especially considering how medical critical care patients are placed in other intensive care units within our institution based on bed availability. Unequal groups would unduly bias the results and make the analysis less meaningful in terms of contributing to the current body of evidence.

Any medication events, including adverse drug reactions or medication errors, will be routinely reported throughout the study to the UTMC Safety Intelligence system. Routine reports of events related to the study will be reviewed weekly by our medication safety office if necessary. Data will be collected continuously throughout the study duration and investigators will review the data for any concerning safety or efficacy differences between the treatment groups. Upon regular screening for adverse drug events, if any are detected, they will be not only be reported to the Safety Intelligence system but will also be reported for review by the IRB.

Per the FDA guidance for clinical investigators regarding the need for an investigational new drug (IND) application in human research studies, investigations are exempt if the drug is lawfully marketed in the U.S., the investigation is not intended to support a new indication or change the labeling of the drug, the investigation will not support a change in advertising for the drug, and the route of administration, dose, or any other factor of the investigation will not increase the risk associated with the drug[7]. Our study, since we are not changing standard of care and are using accepted, studied doses of hydrocortisone and fludrocortisone, meet these criteria for exemption from IND application.

Outcomes:

- Primary Endpoint:
    - Time to resolution of shock (defined as 24 hours vasopressor free)
- Secondary Endpoints:
    - ICU Length of Stay (LOS)
    - Hospital LOS
    - All-cause mortality at ICU discharge
    - All-cause mortality at hospital discharge
    - All-cause mortality at 28 days of admission
    - All-cause mortality at 90 days of admission
    - Withdrawal of treatment therapy during ICU stay
    - Reinitiation of vasopressor therapy (after vasopressor free for 24 hours)
    - Reinitiation of hydrocortisone and/or fludrocortisone
    - Mechanical ventilator free days during ICU admission
    - Duration of steroid therapy
- Safety Endpoints
    - Documentation of two consecutive point of care blood glucose checks >180 mg/dl after initiation of hydrocortisone and/or hydrocortisone/fludrocortisone
    - Gastrointestinal bleed during study period (as documented by provider)
        - Severity of bleed as determined by GUSTO criteria
            - Severe: deadly bleeding; intracerebral bleeding or substantial hemodynamic compromise
            - Moderate: bleeding requiring transfusion
            - Mild: other bleeding not requiring transfusion or causing hemodynamic compromise
    - New initiation of renal replacement therapy during study period
    - Electrolyte abnormalities
        - Sodium level greater than 150 mEq/L during study period
        - Potassium level greater than 5.5 mEq/L during study period

Other Data Collected:

- Demographics: Age, sex, weight, height, BMI, ethnicity (race)
- Septic Shock Bundle initiated
- WBC at time of steroid initiation and at discontinuation

- Initial lactic acid level on admission
- Lactic acid level at initiation of vasopressors
- Vasopressor initiated (norepinephrine, epinephrine, phenylephrine, vasopressin, dopamine, dobutamine)
- Vasopressor dose when steroid therapy was initiated (mcg/min and mcg/kg/min)
- Max vasopressor dose during study period
- SOFA Score
- APACHE Score
- Charlson Comorbidity Index
- Site of infection (lung, intraabdominal, urogenital, skin, CNS, endocarditis, bacteremia, unknown, etc.)
- Non-contaminant, positive culture during study period with clinical correlation to septic shock event
    - Site of culture
    - Gram Positive
    - Gram Negative
    - Viral
    - Fungal
    - Organism
- Comorbidities:
    - Documented heart failure
    - Documented chronic kidney disease stage III-IV not requiring renal replacement therapy at baseline
- Documentation of concurrent cardiogenic shock during study period
- Serum creatinine at initiation of steroid therapy
- Serum creatinine at discontinuation of steroid therapy
- Renal replacement therapy at the initiation of steroid therapy
- Mechanical ventilation at initiation of steroid therapy
- Other systemic steroid use (methylprednisolone, dexamethasone, prednisone) prior to pressor initiation
- Systemic steroid use prior to admission (home medication)
- Continuation of baseline/prior steroid in combination with hydrocortisone/fludrocortisone
- Inhaled corticosteroid use
- Intubation with etomidate
- Amount of diuretics received during study period
- Acute respiratory distress syndrome documented during study period
- Administration of neuromuscular blocker during study period

Statistical Analysis:

Statistical Power

In order to achieve adequate statistical power for the proposed prospective trial, an a priori sample size calculation was completed based on an evidence-based measure of effect size from the APROCCHSS and CORTICUS trials[3,4]. The evidence-based difference between the treatment groups was 24 hours (Group 1 *M* = 96, SD = 36; Group 2 *M* = 72, SD = 36), leading to a Cohen's *d* effect size of 0.67. With a two-tailed hypothesis, an effect size of *d* = 0.67, an alpha value of 0.05, and equal allocation to treatment groups (1:1), 39 participants would be needed for each treatment group. This means the total sample size will be *n* = 78 in order to achieve adequate statistical power for the trial.

Statistical methods

Frequency and percentage statistics will be used to analyze categorical demographic, predictor, confounding, and outcome variables of interest for the sample. Descriptive statistics will be used to describe the sample characteristics associated with continuous variables. The assumption of normality of continuous distributions will be assessed using skewness and kurtosis statistics. If either statistic is above an absolute value of 2.0, then the distribution will be assumed to be non-normal. Homogeneity of variance between independent groups will be tested using Levene's Test for Equality of Variances. When both statistical assumptions are met, independent samples t-tests will be used to compare the treatment groups on continuous outcomes. Means and standard deviations will be reported and interpreted for these analyses. Mann-Whitney U tests will be used for comparisons when statistical assumptions are violated. Medians and interquartile ranges will be presented and analyzed for non-parametric comparisons. Chi-square tests will be used to test for significant associations between the treatment groups and categorical outcomes. Relative risk with 95% confidence intervals will be reported for significant categorical associations. Multiple regression analysis will be performed with time to resolution of shock as the outcome. Linearity, normality, homoscedasticity, multicollinearity, and autocorrelation assumptions for the regression analysis will be performed. Unstandardized beta coefficients, standard errors of the coefficients, and standardized beta coefficients will be reported and interpreted, along with the change in shared variance (R2) and respective F-tests. All analyses will be conducted using SPSS Version 22 (Armonk, NY: IBM Corporation) and statistical significance will be assumed at an alpha value of 0.05.

A priori subanalysis will be performed on the following subset of patients: documented history of heart failure and documented chronic kidney disease stage III and IV requiring renal replacement therapy at baseline.

Critical Analysis/Limitations:

Limitations of this study will include the open-label design without blinding and placebo controls. Also, as data collection will be retrospective in nature, we will be relying on nursing documentation for timing of vasopressor initiation and discontinuation for our primary outcome. This could introduce documentation bias, but it is important to point out that our critical care nursing staff document pressor requirements hourly. Also, to note, previous trials have utilized fludrocortisone 50 mcg doses. Currently, the only commercially available fludrocortisone product in the United States is a 100 mcg tablet. In order to comply with the

previously studied dose and the current guideline recommended therapy, we will be utilizing fludrocortisone 50 mcg in our study. This will be achieved by splitting the available 100 mcg tablet in half. Education will be provided to all providers, pharmacists, and nursing involved in the project about the correct dose for fludrocortisone and the appropriate way to order the dose.

Protected Health Information:
Patients and their specific health information will be de-identified to protect privacy. Any information collected that contains PHI will be stored in a secure, locked area on password-protected electronic files that are only accessible to study investigators. Any information containing PHI will be properly disposed of at the end of the study period.

Study Budget: Cost of printing of notification of research

Timeline:
Estimated October 2018 through July 2019

References:

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